Remarks/Arguments

The foregoing amendments to the claims are of a formal nature, and do not add new matter. Claims 124, 129-131, 135-145 were pending in this application. Claim 139 has been amended to more clearly define what the Applicants consider is their invention. New claims 146-150 have been added which rely on assay 94: inhibition of the uptake of glucose or FFA (free fatty acids) by adipocyte cells.

Errors within the response of February 28, 2005 remarked upon by the Examiner have been presently amended; however since the Examiner indicated that the previous response was not fully responsive, Applicants assume that the amendment filed February 28, 2005 was not entered. Therefore, Applicants retain the marked-up version of the previously amended claims for clarity and request that the present amendments be considered and entered for the record and that the response of February 28, 2005 be disregarded.

Accordingly, Claims 124, 129-131, 135-145 and 146-150 are now pending in this application. The previous rejections are traversed and discussed as applied to the new claims.

Continuity

As asserted previously, Applicants believe they are entitled to an effective filing date of at least **June 23, 1999** based on the gene amplification assay for claims 124, 129-131 and 135-145.

Further, Applicants also rely on assay 94 (detection of polypeptides that affect glucose or FFA uptake by primary rat adipocytes which is well-described at least in Example 158, page 530 of the specification) for patentable utility of nucleic acids encoding PRO1182, which was first disclosed in International Application PCT/US00/08439, filed March 30, 2000, priority to which has been claimed in this application. Hence, Applicants believe that they are entitled to an effective filing date of at least **March 30, 2000** for claims 124, 129-131, 135-138 and new claims 146-150.

Claim Rejections – 35 USC § 101 and §112, first paragraph

Claims 119-126, 129-131 and 135-145 were rejected under 35 U.S.C. §101 for lack of utility.

Claims 119-126, 129-131 and 135-145 were further rejected under 35 U.S.C. §112, first paragraph allegedly since "the claimed invention was not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention".

In the response submitted on December 20, 2004, Applicants had canceled claims 119-123, 125 and 126 and had amended claim 124 to remove references to polypeptides and other variant nucleic acids. Applicants had also submitted a Declaration by Audrey Goddard, Ph.D. to show that a 2-fold increase in DNA copy number is considered significant and had asserted that thus, one skilled in the art would know that claims 124, 129-131, 135-138 and 139-145 would have utility in the detection of squamous lung carcinomas. In this response, Applicants have further amended claim 139 to recite "(a)n isolated nucleic acid molecule consisting of a fragment of the nucleic acid sequence of SEQ ID NO: 356 or a complement thereof.... that specifically hybridizes under stringent conditions" for clarity, that is, to particularly claim what the Applicants consider is their invention. Accordingly, Applicants submit that claims 124, 129-131 and 135-145 have patentable utility at least based on the results presented in the gene amplification assay.

New claims 146-150 rely on assay 94 (inhibition of the uptake of glucose or FFA (free fatty acids) by adipocyte cells) for patentable utility and submit that the specification provides sufficient disclosure to establish a specific, substantial and credible utility for nucleic acids encoding the PRO1182 polypeptide at least in Example 158, page 530 of the specification. The adipocyte glucose/FFA assay of the instant application is performed as follows: primary rat adipocyte cells are plated on a 96 well plate and incubated overnight with media supplemented with PRO1182 polypeptide. After the initial overnight incubation, samples of the media are taken at hour 4 and hour 16 and residual glycerol, glucose and FFA are measured. After the hour 16 sample is taken, insulin is added to the media and the adipocytes are allowed to incubate for an additional 4 hours. After this final 4 hour incubation, another sample is taken and residual glycerol, glucose and FFA is measured again. As a control, identical incubations and samplings are performed on cells that have been incubated overnight in media initially supplemented with insulin rather than PRO1182 polypeptide. Results are scored as positive in the assay if the uptake is greater than 1.5 times (stimulatory) or less than 0.5 time (inhibitory) the uptake of the

insulin control. As PRO1182 resulted in less than 0.5 the uptake of the insulin control, PRO1182 tested positive as an inhibitor of glucose/FFA uptake in adipocyte cells.

The adipocyte glucose/FFA uptake assay was designed to determine whether a polypeptide is capable of modulating, either positively or negatively, the uptake of glucose, or free fatty acids by adipocyte cells. The assay identifies polypeptides that are useful for treating disorders wherein stimulation or inhibition of glucose uptake by adipocytes is therapeutically effective. That is, a protein or agent which directly or indirectly increases glucose transport in this assay is potentially useful in the treatment of metabolic disorders as discussed herein. Therefore, one skilled in the art would readily understand that a protein that inhibits glucose uptake into adipocytes is a therapeutic target, since blocking its function would 'decrease' the inhibition, and thus, increase glucose uptake into adipocytes. One skilled in the art would also know that antagonists, including antisense nucleic acid sequences against PRO1182, which are part of the instant invention, are useful antagonistic agents. Antisense technology is described in detail in the instant specification. Examples of such metabolic disorders where such polypeptides or agents are useful include, but are not limited to, obesity, diabetes, and hyper- or hypo-insulinemia. Therefore, the skilled artisan would readily recognize a utility for PRO1182 polypeptide based on its positive hit in the adipocyte glucose/FFA uptake assay.

Applicants further submit that the glucose/FFA uptake assay, as described in Example 158 of the instant application, was a "well-established assay" around the effective filing date of March 30, 2000. In fact, the art available around the effective filing date of March 30, 2000, strongly provided the necessary nexus between proteins that test positive in the adipocyte glucose/FFA assay and metabolic disease treatment. For example, it was well known in the art well before March 30, 2000 that increased glucose uptake by adipocyte cells was the hallmark of a number of therapeutically effective agents, such as troglitazone and poiglitazone. (Tafuri, *Endocrinology*, 137(11): 4706-4712 (1996); Sandouk, *et al., Endocrinology*, 133(1):352-359 (1993) - copy enclosed with previously submitted IDS). Both troglitazone and poiglitazone are members of the thiazolidinedione class of compounds and have been used to effectively treat noninusulin-dependent diabetes mellitus (NIDDM), the most common form of diabetes. Both compounds were shown to function, at least in part, by increasing the number of cellular glucose transporters in order to facilitate increased glucose uptake.

It had also been shown that 'vanadium salts' could be a potential treatment for diabetes and several clinical trials had already been performed as of the effective filing date of March 30, 2000 (see page 26617, right column, Goldwaser *et al.*, *J. Biol Chem.*, 274(37):26617-26624 (1999) - copy enclosed with previously submitted IDS). Using a rat adipocyte culture system, similar to the system disclosed in the instant application, Goldwaser *et al.* showed that vanadium ligand l-Glu (γ)HXM potentiates the capacity of free vanadium ions to activate glucose uptake and glucose metabolism in rat adipocytes *in vitro* by 4-5 folds and to lower blood glucose levels in hyperglycemic rats *in vivo* by 5-7 folds. Similar assays were commonly used to identify potential anti-diabetic agents and to examine the regulatory mechanisms of important molecules involved in fat cell metabolism.

In another study, Mueller *et al.*, who were interested in determining the influence of glucose uptake on leptin secretion, employed essentially the same assay to measure changes in glucose uptake after insulin exposure. (Mueller *et al., Endocrinology*, 139(2): 551-558 (1998) - copy enclosed with previously submitted IDS). Figure 1A showed the glucose concentrations in medium from 0-96 hours from isolated rat adipocytes in primary culture with various insulin concentrations. As indicated by the decrease in glucose in the medium in the Figure, Mueller *et al.* suggested that insulin produced a concentration-dependent increase in glucose uptake by the cultured adipocytes. Based on these experimental results, the authors stated that insulin increased leptin secretion over 96 hours, and that the increase in leptin was more closely related to the amount of glucose taken up by the adipocytes than to the insulin concentration, suggesting a role for glucose transport and/or metabolism in regulating leptin secretion. (See Abstract).

Using the same assay system, Mueller *et al.* further studied the effect of two well-known anti-diabetic agents, metformin and vanadium, on leptin secretion. These agents were known to enhance glucose uptake. (Muller *et al.*, *Obesity Research,* 8(7): 530-539 (2000) - copy enclosed with previously submitted IDS). Mueller's experimental data indicated that both metformin and vanadium increased glucose uptake and inhibited leptin secretion from cultured adipocytes. Further, as was well known in the art at the time of the instant filing, leptin was involved in the regulation of food intake, energy expenditure and body fat stores (that is, the metabolic status of an organism). As disclosed by Mueller *et al.* (1998) on page 551, column 1, leptin was known to decrease after fasting or caloric restriction and increase several hours after refeeding. Based on

Mueller's teachings, it was known that "agents modulating leptin regulation" would be useful in treating obesity. Thus, taken together along similar lines, one skilled in the art would have known that an inhibitor of adipocyte glucose uptake like PRO1182 would be useful to investigate leptin regulation, and potentially, for obesity treatment.

These studies discussed above clearly established the usefulness of agents identified through the glucose/FFA uptake assay as therapeutic agents for treating metabolic diseases such as obesity, diabetes, hyper- or hypo-insulinemia. In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions that **Office personnel must be careful not to interpret the phrase "immediate benefit to the public"** or similar formulations used in certain court decisions **to mean that products or services based on the claimed invention must be "currently available" to the public** in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a '"substantial" utility'"[1] (emphasis added). Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement states, "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility." Accordingly, Applicants respectfully submit that Applicants' assertion that the claimed PRO1182 proteins have utility in the field of treatment of metabolic diseases such as diabetes, obesity, etc. is substantial.[1]

In view of the above, Applicants respectfully submit that the specification discloses at least one credible, substantial and specific asserted utility for the nucleic acids encoding the polypeptide PRO1182. Further, based on this utility, the disclosure in the specification, the well-established knowledge in the art (at the effective date of filing) regarding agents that modulate or regulate glucose uptake and their usefulness in treatment of metabolic diseases, one skilled in the art would have known how to use the claimed nucleic acids encoding the PRO1182 polypeptide. Accordingly, the Examiner is requested to reconsider and withdraw the present rejection under 35 U.S.C. §101 and §112, first paragraph.

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[1] *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.

Claim Rejections - 35 USC § 112, first paragraph- Written Description

Claims 119-123 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time of filing, had possession of the claimed invention. Applicants respectfully traverse this rejection to the pending claims.

In view of the cancellation of claims 119-123 without prejudice or disclaimer, this rejection is moot and should be withdrawn.

In view of the new claims, Applicants respectfully submit that the instant invention evidences the actual reduction to practice of a full-length PRO1182 of SEQ ID NO: 357, with or without its signal sequence, or encoded by the full-length coding sequence of the cDNA of SEQ ID NO: 356 or which is deposited under ATCC accession number 203088. Further the amended claims recite the functional recitation: "wherein the polypeptide encoded by said nucleic acid inhibits the uptake of glucose or FFA (free fatty acids) by adipocyte cells," which is based on a well-established assay known to the skilled artisan at the effective filing date of this application. Therefore, the polypeptides encoded by the claimed nucleic acids are defined both by functional as well as structural features. As stated above, the Examiner acknowledged that the sequence set forth in SEQ ID NO: 356 meets the written description provision of 35 U.S.C. §112, first paragraph. Thus, the genus of nucleic acids with at least 80% sequence identity to the nucleic acid encoding the SEQ ID NO: 357 or the nucleic acid sequence of SEQ ID NO: 356, wherein the encoded polypeptides possess the functional property of inhibiting the uptake of glucose or FFA by adipocyte cells would meet the requirement of 35 U.S.C. §112, first paragraph, as providing adequate written description.

The instant specification provides methods for determining percent identity between two nucelic acid sequences. In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. The specification describes methods wherein the encoded polypeptides can be tested in an assay that inhibits the uptake of glucose or FFA by adipocyte cells. Thus the description of the claimed genus is achieved. Hence, Applicants respectfully request that this rejection be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-2730P1C64).

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: June 23, 2005

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